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Case Control Study

Socio-economic status and lifestyle factors are associated with achalasia risk: A population-based case-control study

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Abstract

AIM: To evaluate the association between various lifestyle factors and achalasia risk.

METHODS: A population-based case-control study was conducted in Northern Ireland, including $n = 151$ achalasia cases and $n = 117$ age- and sex-matched controls. Lifestyle factors were assessed *via* a face-to-face structured interview. The association between achalasia and lifestyle factors was assessed by unconditional logistic regression, to produce odds ratios (OR) and 95% confidence interval (CI).

RESULTS: Individuals who had low-class occupations were at the highest risk of achalasia (OR = 1.88, 95%CI: 1.02-3.45), inferring that high-class occupation holders have a reduced risk of achalasia. A history of foreign travel, a lifestyle factor linked to upper socio-economic class, was also associated with a reduced risk of achalasia (OR = 0.59, 95%CI: 0.35-0.99). Smoking and alcohol consumption carried significantly reduced risks of achalasia, even after adjustment for socio-economic status. The presence of pets in the house was associated with a two-fold increased risk of achalasia (OR = 2.00, 95%CI: 1.17-3.42). No

childhood household factors were associated with achalasia risk.

CONCLUSION: Achalasia is a disease of inequality, and individuals from low socio-economic backgrounds are at highest risk. This does not appear to be due to corresponding alcohol and smoking behaviours. An observed positive association between pet ownership and achalasia risk suggests an interaction between endotoxin and viral infection exposure in achalasia aetiology.

Key words: Achalasia; Risk factors; Epidemiology; Lifestyle; Socio-economic status

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Core tip: Little is known about achalasia aetiology, with roles suggested for genetic conditions, auto-immune diseases and infectious agents. This population-based case-control study investigated lifestyle and household factors in adulthood and childhood in relation to achalasia risk, for the first time. Results indicate that achalasia is a disease of inequality, and individuals from low socio-economic backgrounds are at highest risk. The burden of achalasia in lower socio-economic groups cannot be explained by smoking or alcohol intake. Pet ownership was associated with a two-fold increased risk of achalasia. Further studies of environmental factors and achalasia risk are warranted.

Coleman HG, Gray RT, Lau KW, McCaughey C, Coyle PV, Murray LJ, Johnston BT. Socio-economic status and lifestyle factors are associated with achalasia risk: A population-based case-control study. *World J Gastroenterol* 2016; 22(15): 4002-4008 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v22/i15/4002.htm> DOI: <http://dx.doi.org/10.3748/wjg.v22.i15.4002>

INTRODUCTION

Oesophageal achalasia is one of the most poorly understood diseases of the digestive tract. Achalasia is a neurodegenerative motility disorder that results in loss of normal lower oesophageal sphincter function and aperistalsis^[1]. Oesophageal manometry is regarded as the ultimate diagnostic investigation for this condition^[1]. Relatively little attention has been given to understanding the underlying aetiology of this disease, and more efforts are needed to ultimately achieve prevention of achalasia.

Although achalasia remains a rare condition, a recent review by our working group suggests that there has been an approximate two-fold increase in incidence since the mid-1980s up to the mid-2000s^[2]. Reports from Canada^[3] and Italy^[4] estimate

that achalasia incidence is now approximately 1.6 per 100000 population. Such a rise in incidence could well reflect changes in diagnostic criteria and increased awareness of achalasia amongst clinicians, however it could also point to a role for changing environmental risk factors over this timeframe.

Previously suggested risk factors for achalasia include genetic and autoimmune conditions^[5,6], and infections such as the Herpes Simplex Virus (HSV-1)^[7,8]. To our knowledge, no lifestyle factors have been investigated in relation to achalasia development. Associations and biologically plausible mechanisms have been reported for lifestyle factors in the role of other neurodegenerative disorders, such as Alzheimer's disease, motor neuron disease and multiple sclerosis^[9-11].

Further, the timing of exposure to environmental risk factors may be important in disease aetiology. Childhood factors have been associated with risk of other oesophageal conditions in later life, including oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma in a series of Danish population-based studies^[12-14]. Exposure to infectious diseases during childhood has also been speculated to contribute to the neurodegenerative Parkinson's disease risk in adulthood^[15]. Given the broad age at diagnosis observed in achalasia cases^[16,17], it would be interesting to study the potential role of childhood factors in achalasia development.

The aim of this novel population-based case-control study was to evaluate the association between exposure to environmental factors throughout the lifespan and risk of oesophageal achalasia.

MATERIALS AND METHODS

Subject recruitment

Patients were identified by records of all individuals undergoing oesophageal manometry performed in the Gastrointestinal Physiology Unit, Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom between 1989-2006. This was the regional centre for oesophageal manometry in Northern Ireland and diagnosed $n = 304$ primary achalasia patients, aged 16 years or older, during that timeframe. Of these, $n = 202$ cases were invited to participate in the study and $n = 151$ cases were successfully recruited (response rate = 74.8%). Population-based controls were identified *via* General Practitioner practices throughout Northern Ireland, and $n = 117$ controls took part in the study from the total $n = 247$ controls invited (response rate: 47.4%). Controls were frequency-matched within groups defined by age (< 50 , $50-69$, ≥ 70 years) and sex to their corresponding cases, therefore similarities in age and sex distribution reflect this study design. This study was ethically approved by the Office for Research Ethics Committees Northern Ireland

Table 1 Descriptive characteristics of achalasia cases and matched controls *n* (%)

| Characteristics | Achalasia cases <i>n</i> = 151 | Controls <i>n</i> = 117 | <i>P</i> value |
|---|-----------------------------------|----------------------------|----------------|
| Age, yr (mean ± SD) | 55.9 ± 17.1 | 55.8 (16.0) | 0.97 |
| Age at diagnosis (mean ± SD) | 47.6 ± 17.8 | / | / |
| Sex | | | |
| Male | 76 (50.3) | 55 (47.0) | 0.59 |
| Female | 75 (49.7) | 62 (53.0) | |
| Previous medical history | | | |
| Ischaemic heart disease | 12 (8.0) | 7 (6.0) | 0.53 |
| Diabetes Mellitus | 4 (2.7) | 3 (2.6) | 0.97 |
| Hypertension | 27 (17.9) | 17 (14.5) | 0.46 |
| Hypercholesterolaemia | 16 (10.6) | 12 (10.3) | 0.93 |
| Asthma/COPD | 11 (7.3) | 4 (3.4) | 0.17 |
| Gastritis/Peptic ulcer | 19 (12.6) | 8 (6.8) | 0.12 |
| Autoimmune/Connective Tissue Disorders | 1 (0.7) | 1 (0.9) | 0.86 |
| Family history of achalasia | 5 (3.3) | 0 (0.0) | 0.05 |
| Number of years in education (mean, SD) | 12.5 (3.3) | 12.8 (3.1) | 0.34 |
| Occupation class | | | |
| High | 39 (25.8) | 45 (38.5) | 0.17 |
| Medium | 47 (31.1) | 32 (27.4) | |
| Low | 55 (36.4) | 34 (29.1) | |
| Not classified | 10 (6.6) | 6 (5.1) | |

COPD: Chronic obstructive pulmonary disorder.

(ORECNI). Written informed consent was obtained from all study participants.

Assessment of clinical and demographic factors

Information on demographic data, lifestyle factors, past medical history, family history, childhood factors, medications and previous achalasia treatment, were collected by an interviewed questionnaire, administered by one of two trained interviewers who were not blinded to the case-control status of individuals. Socio-economic status was derived from occupation data, according to National Statistics Socio-Economic Classification as used by the Office for National Statistics^[18]. Briefly in this classification system, professional, employer or manager occupations are considered to be high class; intermediate or junior non-manual occupations are categorised as medium class; skilled, semi-skilled or unskilled manual occupations are considered to be low class; students or not employed are considered as unclassified^[18].

Statistical analysis

Statistical analysis comparing continuous or categorical variables between achalasia cases and controls was conducted using an independent *t*-test or chi-squared test, respectively. Odds ratios (OR) and corresponding 95% confidence interval (CI) were generated using unconditional logistic regression models to assess achalasia risk according to childhood and adult socio-demographic and lifestyle factors. Both unadjusted and adjusted regression models were performed, with the latter adjusting for age, sex, and socio-economic

status (for adulthood factors) as potential confounders. Interaction between socio-economic status, smoking and alcohol status to influence achalasia risk was assessed using the likelihood ratio test. All statistical analysis was performed using Stata Version 11.2 (StataCorp, College Station, TX, United States).

RESULTS

Comparison of characteristics between achalasia cases and controls is shown in Table 1. Mean age at interview was 55.9 years for achalasia cases, of whom 50% were male. Cases were, on average, recruited 8.3 years after their incident diagnosis of achalasia. No significant differences in education, occupation or previous medical history were detected between cases and controls (Table 1), with exception of a family history of achalasia which was more prevalent in achalasia cases.

Table 2 shows the association between childhood household factors and achalasia risk. No significant associations were detected for number of rooms, household density or toilet location in the childhood home, and risk of achalasia. A non-significant inverse association was observed between the presence of smokers in the childhood home, and achalasia risk (OR = 0.85, 95%CI: 0.48-1.50). Non-significant increased risks of achalasia were also noted for childhood homes in which a pet was present (OR = 1.17, 95%CI: 0.67-2.04), and for low compared with high socio-economic households, as determined by occupation of head of household (OR = 1.64, 95%CI: 0.78-3.67). Having been breastfed did not seem to influence achalasia risk. Further adjustment for age and sex had little impact on observed associations.

The association between achalasia risk and various adult socio-demographic and lifestyle factors is shown in Table 3. The presence of pets in the house was associated with an almost two-fold increased risk of achalasia (OR = 1.92, 95%CI: 1.12-3.31). Years of education completed were unrelated to achalasia risk. However, individuals who had low-class occupations were at the highest risk of achalasia (OR = 1.88, 95%CI: 1.02-3.45), inferring that high-class occupation holders have a reduced risk of achalasia. A history of foreign travel, a lifestyle factor linked upper socio-economic class, was also associated with a reduced risk of achalasia (OR = 0.59, 95%CI: 0.35-0.99).

Smoking and alcohol consumption carried significant reduced risks of achalasia, even after adjustment for socio-economic status (Table 3). The potential interaction between alcohol, smoking and socio-economic status to influence achalasia risk was further explored in stratified analysis (data not shown). Reduced statistical power resulted in a lack of statistically significant findings. However, the reduced risk of achalasia for alcohol consumers and

Table 2 Early life and childhood household factors and achalasia risk *n* (%)

| Early life risk factors | Achalasia cases <i>n</i> = 151 | Controls <i>n</i> = 117 | Unadjusted OR (95%CI) | Adjusted ² OR (95%CI) |
|--|-----------------------------------|----------------------------|--------------------------|-------------------------------------|
| Number of rooms | | | | |
| < 6 | 71 (47.0) | 54 (46.2) | 1 | 1 |
| ≥ 6 | 80 (53.0) | 63 (53.8) | 0.97 (0.60-1.57) | 0.96 (0.59-1.57) |
| Number of bedrooms | | | | |
| < 3 | 35 (23.2) | 29 (24.8) | 1 | 1 |
| ≥ 3 | 116 (76.8) | 88 (75.2) | 1.09 (0.62-1.92) | 1.09 (0.61-1.96) |
| Household density | | | | |
| < 2 | 55 (36.4) | 44 (37.6) | 1 | 1 |
| ≥ 2 | 96 (63.6) | 73 (62.4) | 1.05 (0.64-1.73) | 1.05 (0.64-1.73) |
| Toilet location | | | | |
| Indoors | 85 (56.3) | 73 (62.9) | 1 | 1 |
| Outdoor | 66 (43.7) | 43 (37.1) | 1.32 (0.80-2.16) | 1.55 (0.85-2.82) |
| Presence of smokers | | | | |
| No | 38 (25.2) | 26 (22.2) | 1 | 1 |
| Yes | 113 (74.8) | 91 (77.8) | 0.85 (0.48-1.50) | 0.85 (0.48-1.52) |
| Presence of any pets in the house ¹ | | | | |
| No | 36 (23.8) | 31 (26.5) | 1 | 1 |
| Yes | 115 (76.2) | 86 (73.5) | 1.15 (0.66-2.31) | 1.17 (0.67-2.04) |
| Occupation of head of household | | | | |
| High | 15 (9.9) | 18 (15.4) | 1 | 1 |
| Medium | 56 (37.1) | 40 (34.2) | 1.68 (0.76-3.73) | 1.70 (0.77-3.79) |
| Low | 78 (51.7) | 57 (48.7) | 1.64 (0.76-3.53) | 1.69 (0.78-3.67) |
| Unclassified | 2 (1.3) | 2 (1.7) | 1.20 (0.15-9.57) | 1.25 (0.15-10.23) |
| Breastfed | | | | |
| No | 63 (41.7) | 48 (41.0) | 1 | 1 |
| Yes | 61 (40.4) | 51 (43.6) | 0.91 (0.54-1.55) | 0.89 (0.49-1.59) |
| Unknown | 27 (17.9) | 18 (15.4) | 1.14 (0.56-2.31) | 1.12 (0.54-2.31) |

¹Compared with no pets present in the childhood house; ²Adjusted logistic regression model includes age (at interview) and sex.**Table 3** Early life and childhood household factors and achalasia risk *n* (%)

| Risk factors | Achalasia cases <i>n</i> = 151 | Controls <i>n</i> = 117 | Unadjusted OR (95%CI) | Adjusted OR ¹ (95%CI) |
|--|-----------------------------------|----------------------------|-----------------------|-------------------------------------|
| Occupation class | | | | |
| High | 39 (25.8) | 45 (38.5) | 1 | 1 |
| Medium | 47 (31.1) | 32 (27.4) | 1.69 (0.91-3.15) | 1.75 (0.93-3.29) |
| Low | 55 (36.4) | 34 (29.1) | 1.87 (1.02-3.42) | 1.88 (1.02-3.45) |
| Unclassified | 10 (6.6) | 6 (5.1) | 1.92 (0.64-5.77) | 1.90 (0.59-6.14) |
| Years in education | | | | |
| < 13 yr | 91 (60.3) | 64 (54.7) | 1 | 1 |
| ≥ 13 yr | 60 (39.7) | 53 (45.3) | 0.80 (0.49-1.30) | 0.92 (0.52-1.61) |
| Smoking status | | | | |
| Non-smoker | 91 (60.3) | 61 (52.1) | 1 | 1 |
| Former smoker | 36 (23.8) | 28 (23.9) | 0.86 (0.48-1.56) | 0.82 (0.44-1.54) |
| Current smoker | 24 (15.9) | 28 (23.9) | 0.57 (0.30-1.08) | 0.47 (0.24-0.92) |
| Alcohol consumer | | | | |
| No | 58 (38.4) | 31 (26.5) | 1 | 1 |
| Yes | 93 (61.6) | 86 (73.5) | 0.58 (0.34-0.98) | 0.55 (0.32-0.95) |
| Combined alcohol/smoking status | | | | |
| Non-drinker and Non-smoker | 46 (30.5) | 20 (17.1) | 1 | 1 |
| Drinks alcohol or ever smoker | 57 (37.8) | 52 (44.4) | 0.48 (0.25-0.91) | 0.48 (0.25-0.93) |
| Drinks alcohol and ever smoker | 48 (31.8) | 45 (38.5) | 0.46 (0.24-0.90) | 0.41 (0.21-0.83) |
| History of foreign travel outside Europe | | | | |
| No | 96 (63.6) | 58 (49.6) | 1 | 1 |
| Yes | 55 (36.4) | 59 (50.4) | 0.56 (0.34-0.92) | 0.59 (0.35-0.99) |
| Presence of any pets in the house | | | | |
| No | 37 (24.5) | 44 (37.6) | 1 | 1 |
| Yes | 114 (75.5) | 73 (62.4) | 1.86 (1.10-3.14) | 1.92 (1.12-3.31) |

¹Adjusted logistic regression model includes age (at interview), sex and socioeconomic status.

ever smokers remained evident across the three socio-economic groupings (OR = 0.39, 0.61 and 0.44). The reduced risk appeared to be somewhat driven by smoking in low-class occupation holders, and alcohol consumption in high-class occupation holders, however formal tests for interaction were not statistically significant.

DISCUSSION

The results from this novel population-based study suggest that achalasia disproportionately affects individuals from lower socio-economic backgrounds. Smoking and alcohol intake do not explain this inequality in achalasia risk. Pet ownership in adulthood was associated with an increased risk of achalasia, and raises interesting hypotheses about potential explanatory biological mechanisms for achalasia. None of the childhood factors evaluated were associated with achalasia risk, suggesting that early life exposures do not have a role in achalasia development.

This is the first study to assess the relationship between socio-economic status and achalasia. Our findings indicate an increased risk of developing achalasia in individuals with lower socio-economic status. Our results also demonstrate that this is not explained by the "usual" factors associated with lower socio-economic status, namely smoking and alcohol. Instead these factors carry a reduced risk. There is little evidence of biologically plausible mechanisms to link smoking and alcohol to a reduced risk of achalasia - in contrast, nicotine exposure is known to induce loss of lower oesophageal sphincter function^[19]. The findings for smoking and alcohol are highly likely to reflect reverse causation bias, since the majority of achalasia cases in this study were prevalent cases who may have avoided these lifestyle factors to alleviate symptoms. However, such bias is unlikely to have occurred to the extent whereby it is masking an increased risk of achalasia, and recall bias is unlikely to influence the other characteristics enquired about in this study. There are several other plausible associations for the link with lower socio-economic status which merit further exploration.

Firstly, lower socio-economic status is associated with increased gastro-intestinal infection risk in this region^[20]. One hypothesis for the aetiology of achalasia is of a neurotropic virus showing predilection for the squamous mucosa of the oesophagus and targeting the myenteric plexus. There has been some evidence supporting this link in the herpes virus family^[8,21] and a large Spanish study has recently demonstrated increased herpes zoster prevalence/incidence in subjects with lower socio-economic status^[22]. Secondly, autoimmunity has been suggested as a factor in the development of achalasia. Although our study found no significant increase in auto-immune diseases among achalasia patients, this has been demonstrated previously^[6] and there is strong evidence linking auto-

immune disease and lower socio-economic status^[23]. Thirdly, the direct association with occupation (but not education) as a reflection of socio-economic status may reflect exposure to occupational hazards that play a role in achalasia aetiology, for example metal exposure has been linked with Parkinson's disease^[15]. Finally, a hypothesis that has not previously been suggested relates to perinatal factors. Low birth weight has been associated with other oesophageal diseases^[12-14] and is linked with lower socio-economic status^[24]. Recent epigenetic studies have demonstrated methylation changes in the perinatal period, linked to lower socio-economic status and low birth weight babies^[25]. The authors suggest that this is a key element in the development of subsequent disease in adulthood^[25].

We were unable to assess birth weight and other perinatal factors in this study. However, we were able to evaluate other early childhood factors in relation to achalasia risk. No associations were identified between household density, toilet location or history of having been breastfed and achalasia risk. This contrasts with hypotheses that household crowding and resultant earlier/more frequent exposure to infections and antigens could protect against immune-related diseases, as has been noted for Type 1 diabetes^[26,27]. The lack of association suggests that, even if a role for infectious agents does exist for achalasia, the timing of exposure in early childhood may be irrelevant. Three other childhood factors investigated also showed non-significant associations with achalasia, but the direction of associations parallel those seen for adult lifestyle factors. This includes the presence of smokers in the childhood home, which was non-significantly inversely associated with risk, while lower socio-economic occupations held by the head of the childhood household and owning a pet in childhood both carried a non-significant increased risk of achalasia.

Pet ownership in adulthood was associated with an increased risk of achalasia in this study. Evidence to suggest an association between pet ownership and the incidence of other immune-related conditions, such as rheumatoid arthritis and multiple sclerosis (MS), is conflicting^[28-32]. Pet ownership may increase exposure to parasitic infections^[29], and while secondary achalasia is due to parasitic infection with *Trypanosoma cruzi*^[33], there is no evidence to suggest a direct parasitic cause in primary achalasia. Finally, households with resident pets have higher levels of pro-inflammatory endotoxin in the house dust^[34]. Endotoxin is speculated to be hypoallergenic and thereby protect against atopic conditions^[34]. However, as part of a separate mechanistic pathway, endotoxins may interact with viral infection to induce an inflammatory response^[35]. For example, lipopolysaccharide can increase expression of a survival protein (BAG3) that regulates the replication of HSV-1 and Varicella-Zoster virus^[36], and so may act to exacerbate the impact of such viruses on achalasia

development. The finding of an increased risk of achalasia with pet ownership in the current study may also be due to chance, but is unlikely to be due to recall bias. Our observed inverse association between a history of foreign travel outside of Europe, even after adjustment for socio-economic status, may also reflect exposure to an unknown infectious agent that is actually protective against achalasia development.

One of the strengths of the study is that a large number of patients with primary achalasia were recruited into the study using a population-based approach. The response rate among cases was high (75%), suggesting excellent generalisability to the wider population of patients with primary achalasia. Also, to our knowledge, this is the first case-control study investigating potential environmental risk factors in primary achalasia, providing novel insight into mechanisms and potential prevention strategies for this incurable disease.

Certain potential limitations of this study must be acknowledged. Firstly, self-reported risk factors were relied upon in this study, and may be subject to recall and socially-desirable respondent bias. This is likely to explain the significant inverse association for smoking, alcohol and achalasia risk to some extent, but is unlikely to be masking a converse positive association for these lifestyle factors and achalasia risk. Certain factors such as family history were not verified with general practitioners or other medical records. The low response rate of controls (47%) may have introduced bias if the characteristics and exposures of the non-responders were different. Unfortunately, there was no access to medical records of non-responders to compare with responders to allow evaluation of this. The case-control nature of the study design also presents an opportunity for reverse causation to be skewing some of the observed associations, whereby achalasia cases may have altered their habits relating to certain risk factors, due to their disease and symptom experience. However, these limitations affect all epidemiological case-control studies, and we still believe that our analysis provides a useful and novel insight into potential modifiable risk factors for achalasia. Further case-control and cohort studies verifying our results are required.

In conclusion, achalasia appears to be a disease of inequality that disproportionately affects individuals from low socio-economic backgrounds. This does not appear to be due to corresponding alcohol and smoking behaviours. An observed positive association between pet ownership and achalasia risk may lend support to a role for interaction between endotoxin and viral infection exposure in achalasia aetiology. Further studies of environmental factors and achalasia risk are warranted.

COMMENTS

Background

Oesophageal achalasia is one of the most poorly understood diseases of the digestive tract. Achalasia is a neurodegenerative motility disorder that results in loss of normal lower oesophageal sphincter function and aperistalsis. Relatively little attention has been given to understanding the underlying aetiology of this disease, and more efforts are needed to ultimately achieve prevention of achalasia.

Research frontiers

To our knowledge, no lifestyle factors have been investigated in relation to achalasia development. Associations and biologically plausible mechanisms have been reported for lifestyle factors in the role of other neurodegenerative disorders. The aim of this novel population-based case-control study was to evaluate the association between exposure to environmental factors throughout the lifespan and risk of oesophageal achalasia.

Innovations and breakthroughs

Achalasia disproportionately affects individuals from low socio-economic backgrounds. This does not appear to be due to corresponding alcohol and smoking behaviours. An observed positive association between pet ownership and achalasia risk may lend support to a role for interaction between endotoxin and viral infection exposure in achalasia aetiology.

Applications

This is the first study to evaluate environmental risk factors for achalasia, and raises interesting hypotheses about potential explanatory biological mechanisms for achalasia. Further studies of environmental factors and achalasia risk are warranted.

Peer-review

Coleman *et al* present a questionnaire based populational enquiry about risk factors for achalasia. The topic is interesting and some data is original. The authors discussed their findings well.

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